DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Michele M. Hardy
Senior Director, U.S. Regulatory Affairs, GlaxoSmithKline
P.O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

RE: NDA 21-319
AVODART® (dutasteride) Soft Gelatin Capsules
MACMIS # 17228

Dear Ms. Hardy:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a 60-second direct-to-consumer (DTC) broadcast television advertisement (TV ad) entitled "Planetarium" (AVV078R0) for AVODART® (dutasteride) Soft Gelatin Capsules (Avodart) submitted by GlaxoSmithKline (GSK) under cover of Form FDA 2253. The TV ad presents misleading comparative claims and overstates the efficacy of Avodart. Thus, the TV ad misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and FDA's implementing regulations. See 21 U.S.C. 352(n); 21 CFR 202.1(e)(6)(i) & (e)(6)(ii).

Background

According to its FDA-approved product labeling (PI), Avodart is a synthetic 4-azasteroid compound that is a selective inhibitor of steroid 5α-reductase (5AR), an intracellular enzyme that converts testosterone to 5α-dihydrotestosterone (DHT). DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland. According to the INDICATIONS AND USAGE section of the PI, Avodart is approved for the following indication:

> [F]or the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to:
> - improve symptoms,
> - reduce the risk of acute urinary retention (AUR), and
> - reduce the risk of the need for BPH-related surgery.

In addition, the CLINICAL STUDIES section of the PI states (in pertinent part):

> **Effect on Prostate Volume: . . .** Statistically significant differences (AVODART versus placebo) were noted at the earliest post-treatment prostate volume measurement in each study (Month 1, Month 3, or Month 6) and continued through Month 24. At Month 12, the mean percent change in prostate volume across the 3 studies pooled was -24.7% for dutasteride and -3.4% for placebo; the mean difference (dutasteride minus placebo) was -21.3% (range, -21.0% to -21.6% in each of the 3 studies, $p<0.001$). At

> Month 24, the mean percent change in prostate volume across the 3 studies pooled was -26.7% for dutasteride and -2.2% for placebo with a mean difference of -24.5% (range, -24.0% to -25.1% in each of the 3 studies, p<0.001). . . . The reduction in prostate volume seen during the first 2 years of double-blind treatment was maintained throughout an additional 2 years of open-label extension studies.

Misleading Comparative Claims

The TV ad misleadingly suggests that Avodart is superior to other drug therapies when this has not been demonstrated by substantial evidence or substantial clinical experience. Specifically, the TV ad states:

- "So when my doctor said that my going and going could get worse because my prostate was growing I said 'How can we shrink it?'"
- "He said 'AVODART.'"
- "**AVODART is different** because over time it actually shrinks the prostate, so I go less often. **Other medicines, they don't treat the cause, because they don't shrink the prostate**." (emphasis added)

The TV ad clearly suggests that Avodart is the only medication that shrinks the prostate, when this is not the case. Proscar (finasteride) is another 5α-reductase inhibitor approved for the treatment of symptomatic BPH to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of the need for BPH-related surgery. Proscar also reduces prostate volume. Therefore, the claim, "Other medicines . . . don't shrink the prostate" is misleading.

In indentifying Avodart as the only drug that "treats the cause" by shrinking the prostate, the TV ad clearly suggests that Avodart works better than other medications, presumably including drugs with different mechanisms of action that "don't treat the cause," but also including finasteride, which has the same mechanism of action. Avodart is indicated to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of the need for BPH-related surgery. Other products are also indicated to treat the symptoms of BPH and nothing in the labeling for Avodart suggests any specific advantage. FDA is not aware of any comparative clinical trials of Avodart monotherapy and other products approved for the treatment of BPH to support the implication that Avodart is superior to such other products.

Overstatement of Efficacy

The graphic images and verbal statements in the TV ad overstate the efficacy of Avodart therapy with respect to the results one can expect from Avodart. The magnitude of the change depicted in the visuals showing a large planet and a small planet (representing the actor's prostate) overstates the efficacy of Avodart by showing a degree of reduction in prostate volume due to treatment with Avodart that has not been demonstrated by substantial evidence or substantial clinical experience. According to the CLINICAL STUDIES section of the PI for Avodart, "At Month 12, the mean percent change in prostate volume across the 3 studies pooled was -24.7% for dutasteride and -3.4% for placebo . . . At Month 24, the mean

percent change in prostate volume across the 3 studies pooled was -26.7% for dutasteride and -2.2% for placebo." The visual of the planet shrinking in size represents a reduction in prostate volume that is much greater than the reduction actually achieved with Avodart therapy in clinical trials. In fact, the approximately 20 – 25% reduction in volume corresponds to a difference in diameter of less than 10%.

Conclusion and Requested Action

For the reasons discussed above, the TV ad is misleading in violation of the Act and FDA implementing regulations. See 21 U.S.C. 352(n); 21 CFR 202.1(e)(6)(i) & (e)(6)(ii).

DDMAC requests that GSK immediately cease the dissemination of violative promotional materials for Avodart such as those described above. Please submit a written response to this letter on or before March 4, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for Avodart as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 17228 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Avodart comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Cynthia Collins, Ph.D.
Consumer Safety Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Cynthia Collins

2/18/2009 02:35:52 PM